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Primary prevention as an essential factor ensuring sustainability of health systems: the example of congenital anomalies

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Abstract
Protection of early development contributes to health of next generations. Congenital anomalies (and other adverse reproductive outcomes) are an important public health issue and early indicator of public health risks, as early development is influenced by many risk factors (e.g., nutrition, lifestyles, pollution, infections, medications, etc). Effective primary prevention requires an integrated "One Health" approach, linking knowledge and action. This requires surveillance of health events and potential health-damaging factors, science-based risk analysis, citizens' empowerment and education of health professionals. From the policy standpoint, joint budgeting mechanisms are needed to sustain with equity intersectoral actions (involving policy domains of health, social affairs, education, agriculture and environment). States should devote resources to strengthen registries and systematic data collection for surveillance of congenital anomalies, to better inform national prevention strategies. Investing in primary prevention based on scientific evidence is essential to support sustainable and resilient health systems and sustainable development of the society.

Key words
- primary prevention
- sustainability
- resilience
- health promotion
- birth defects

INTRODUCTION

Primary prevention in public health and in the field of rare diseases

Since Hyppocrates, public health care means that, besides treating disease when it occurs, science and actions should reduce the occurrence of diseases. This is specifically called "prevention". *Primary prevention* includes the actions aimed at avoiding the onset of the disease. This means intervening before health effects occur, through measures modifying risk factors, their distribution or the way they reach the individual, for instance by banning substances or conditions known to be associated with one or more disease or adverse health status. Primary prevention, thus, results on eradicating, eliminating or minimizing the impact of disease and disability on the population, through interventions that are applied before there is any evidence of disease or injury, by controlling causative risk factors; the main focus are disease risk factors, in order to reduce the disease incidence.

Reducing disease incidence means a healthier society, while reduced disease burden means improved life quality and working capacity, reduction of avoidable disabilities and mortality, and lower costs for diagnosis and treatments, among other advantages, for the individual as well as for the society. Thus, strengthening and implementing primary prevention with the support of scientific evidence makes the healthcare system more efficient and sustainable, while providing significant benefits to society as a whole, apart from the individual tangible and intagible advantages.

The different and relevant disciplines and actors involved in primary prevention often tend to think and operate in silos [1], concentrating on specific determinants such as lifestyles or living environment. Indeed, the actual problems call for an integration and cross-fertilization among different expertise fields. For instance, communities with low socio-economic status are more prone to live in more polluted settings, with insufficient availability of green areas or healthy food purchases. Therefore, it is also important to gather accurate data that can be analysed wisely to avoid confounding and to properly assess possible interactions of different vari-

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ables and linked factors. These accurate analyses will have an impact on the identification of risk factors and the delineation of primary prevention measures.

It is important to note that, although primary prevention makes the health systems more sustainable, and despite its recognized major role among public health actions, paradoxically it does not attract a corresponding fraction of resources devoted to health by policy makers. For instance, countries from the European Union (EU) overall allocate less than 3% of healthcare expenditure, and as low as 1% in some countries, to primary prevention actions [2].

The reduction of risk factors for poor health outcomes may involve actions beyond the specific domain of healthcare systems. The capacity to fulfill the primary requirements (food security, housings), the quality and safety of living environment (air, water, food), the social environment (education, income, lifestyles), the decisions of policy makers (in what refers to resources devoted to health services), are all determinants involved in increasing or reducing threats for health. In principle, policies should consider their potential impact on health and undergo "health-proofing", as recently implemented in Ireland and a few other EU Countries.

The 2013 Annual Growth Survey [3] recognised that "in the context of the demographic challenges and the pressure on age-related expenditure, reforms of healthcare systems should be undertaken to ensure cost-effectiveness and sustainability, assessing the performance of these systems against the twin aim of a more efficient use of public resources and access to high quality healthcare". The assessment of healthcare policies should be more prevention-oriented. Effective prevention is evaluated on the basis of "diseases avoided". This means that fit-to-purpose sets of performance indicators and outcome measurements should be developed accordingly to better plan future programs and strategies.

When extending the considerations on primary prevention to rare diseases, congenital anomalies (CA) represent a proper field of reflection and action. Many rare diseases are congenital because they result from alteration of prenatal development. This means that their manifestations are present at birth or can be even evident before the delivery. In fact, prenatal diagnosis is possible for many of them. CA, also known as birth defects, are defined by the World Health Organization (www.who.int/topics/congenital_anomalies/en/) as structural or functional anomalies that occur during intrauterine life and can be identified prenatally, at birth or later in life. Indeed, CA represent an important fraction of rare diseases and, at the same time, most CA can be considered rare diseases, based on their frequency [4]. They represent a significant health burden, leading to an overall increased morbidity and to a considerable risk for premature death among affected people, as well as for lifelong disabilities and dependence in many surviving cases [4]. CA's presence since birth or earlier implies that they, and their consequences, must be faced from that early point in life, Due to the critical role of non-genetic factors in their etiology, CA are the main group of rare diseases in which primary prevention measures have a known beneficial impact. Indeed, since 2013 the European Union has endorsed a body of evidence-based *Recommendations* for primary prevention of CA [5]. These recommendations may be relevant to other adverse pregnancy outcomes as well (prematurity, stillbirths, developmental delays and related disabilities), and even they can have an impact on parents' health (since for instance modifying lifestyles or adopting better protection in the workplace will also benefit them), as non-genetic risk factors are frequently shared. The Recommendations [5] discussed the different institutional and societal levels relevant for developing and implementing primary prevention strategies.

MATERIALS AND METHODS

The paper reviews the main literature available on the primary prevention of rare diseases, with a special focus on CA. Several medical databases and additional information resources were utilised and included government documents, reports from international bodies such as the World Health Organisation, and academic studies. The key search terms were primary prevention, congenital anomalies and rare diseases, from 2000 through January 2018. Articles of interest were reviewed to determine which were relevant and subjected to analysis. Selected papers were later used to extrapolate the most relevant messages about primary prevention of on CA.

RESULTS

The reviwe showed that the importance of CA on public health is clear: Christianson *et al*. [6] estimated that overall 7.9 million children are born each year with serious CA of genetic or partially genetic (multifactorial, gene-environment) origin, and additional hundred thousand more are born with serious CA of post-conception origin. In general, and depending on the population considered, it is estimated that approximately 3-6% of newborn infants worldwide are affected by serious CA [7-9]. Moreover, according to the 2015 Global Burden of Disease study, CA led to 8.5% (7.7-9.5%) of deaths under the age of 5 years in 2015 [10], and at least 3.3 million children under 5 years of age die from CA each year [9]. CA represented the most important cause of death below 5 years of age in countries with low and very low under-5 mortality [11]; in addition, Oza *et al* [12] observed that the proportion of deaths from CAs was relatively stable across their study period (data for 2000-2013 in 194 countries), showing the smallest relative decrease in risk compared to other causes (e.g., infections); some authors have estimated that mortality due to CA for the under-5 age group is likely to be a four-fold underestimate [13]. Beyond mortality, an estimated 3.2 million of those who survive may be disabled for life [9]; disability-adjusted life-years (DALY) rates due to CA have increased lately [14]; the years lived with disability (YLD) have increased for CA [15]. Terminations of pregnancy for CA were almost three times more frequent than infant deaths and stillbirths with CA combined [16], and this affects the Global Burden of Disease figures and their interpretation.

These eloquent figures, matched with their intrauterine origin and the major role of non-genetic factors, enhance the interest of their study within the field of rare

diseases, and make them priority targets for research [17] and prevention. Primary prevention of CA is feasible because scientific evidence points to several risk factors (e.g., obesity, infectious and toxic agents) and protective factors (e.g., folic acid supplementation and glycemic control in diabetic women) [18].

The bullet points below summarize the main fields pertinent to primary prevention of CA, encompassing both health systems and policies in relevant fields:

- Actions to mitigate *low socio-economic status and poor education* might have an impressive impact on a number of critical determinants, such as lifestyles (tobacco smoking and alcohol drinking during pregnancy, among others), and unbalanced diet associated with the increased risk of overweight/obesity, which, in its turn, is a significant risk factor for CA.
- *Lifestyles* can partly be tackled by specific policies, whose effectiveness should be evaluated in the context of specific countries. It is critical to reduce the consumption of energy-dense foods and drinks, tobacco and alcohol: a combination of policy actions and individual empowerment, starting from school, seems a suitable general approach. For instance, in Italy, smoking in public places, including the workplace, has been forbidden by law in 2003: the law, matched with publicly-supported anti-smoking advertising, has been received by society with a favourable attitude and has contributed to reduce the number of smokers and especially the environmental exposure to passive smoking. Indeed, as already pointed out, exposure to tobacco smoking is a risk factor for CA and other adverse pregnancy outcomes.
- Low socio-economic status and poor education are associated with a reduced access to *correct information* about health-protecting and health-promoting behaviours, such as the periconceptional supplementation with folic acid, and other preconception care measures.
- The schooling system can play a major role in reducing health inequalities due to different socio-economic status and promoting health awareness and empowerment. The *promotion of health literacy programmes* since primary school can support the adoption of a healthy lifestyle from childhood; a timely empowerment during school age toward correct lifestyles and behaviors may significantly reduce the risk factors for CA in the next generation.
- Actions to control and reduce the exposure to *pollutants in living environment, workplace and foods*: the current EU regulations on *hazardous chemicals* (e.g., the REACH regulation [19]) put emphasis on the identification and management of developmental toxicants. The EU food safety is possibly the domain where prevention and control of pollutants is most developed: however, emphasis needs to be put on the identification of emerging risks [20]. In particular, food safety systems should exploit the available knowledge to improve prevention of long-term risks along the whole food chain, such as those related to endocrine disrupting substances [21]. Full implementation of the EU regulations, currently the world's most advanced ones, calls for a balance between scientific evidence, a reasonable use of the precautionary principle and the necessary involvement of the industrial and agro-food sectors.
- Pollution is not evenly distributed throughout the EU population: a number of *areas are highly exposed* to releases from toxic industrial activities and/or chemical waste from different sources (e.g., petrochemicals or persistent and bioaccumulative –"legacy" – contaminants). In communities with higher exposure to these hazardous chemicals in living environment, CA (together with other adverse reproductive outcomes) represent an important public health issue [22]. As shown, for instance, in Italy by Sentieri, a Istituto Superiore di Sanità-led project. CA are also a sensitive sentinel for environmental quality [23], due to the relatively short latency time and the high susceptibility of the intrauterine life to major toxicological modes of action, such as endocrine disruption.
- The majority of the EU population aged between 18 and 65 years spends over half of their lives at the *workplace*. Workplace represents a diversified environment where exposures through multiple physical, chemical and biological agents can occur: to date women at fertile age are involved in every job role in the EU. But importantly, also men can be exposed to these hazards in the workplace, therefore their gametes will form and mature in an environment that can have an impact on the risk for gene mutations as well as on fertility. Effective prevention and health monitoring interventions in the workplace should be achieved through the co-operative involvement of employers, workers, occupational health professionals and legislators. Health and societal policies should recognize the basic right for a workplace environment that minimizes the health risks for workers as well as for their offspring.
- *Chronic diseases* such as diabetes, *infectious diseases* such as rubella and the emerging Zika viruses, as well as the inappropriate use of certain drugs, such as the antiepileptic drugs with known teratogenic efects, among others, are recognized risk facts for CA. Such risk factors can be significantly mitigated by functioning and accessible *healthcare services*. Hence, actions of top relevance for the protection of the generation(s) to come include the *care for maternal chronic diseases* (e.g., diabetes, epilepsy), the deliverance of *vaccination programmes* (e.g., toward rubella) and the enforcement of *pharmacovigilance programmes*. These measures are supported by *teratology information services* where the different actors involved in primary prevention (health care professionals and lay people) can solve their questions on the different risks and possible measures. Such policies could also receive a significant support by fostering the consistent involvement of pharmacists and nurses.
- *Pre-conception care* is surely the most effective way to put in practice all the known measures for primary prevention of CA, adapting them to the specific characteristics of each couple. Therefore, policies should put special focus on the establishment of services specifically devoted to this approach by which risk factors can be identified, the most appropriate measures

can be adopted accordingly, the most convenient information can be provided (adapted to the specific characteristics of each couple of parents to be) by health care workers or specialists, and some preventive measures can be put in practice.
- *Pregnancy planning* is another pivotal issue, that should be promoted by all means.
- The inadequate *access to health services* may be a special concern for low-status population groups and/or groups considered as "marginal" (immigrants, gypsies and other social-cultural groups, isolated communities). The primary prevention of CA in such population groups may require, therefore, specific attention and *ad hoc* actions.
- Health systems include *data collection and surveillance*: CA and rare disease registries of adequate quality can provide a valuable support to prevention strategies, e.g., by allowing ad hoc studies in order to assess potential risk factors (maternal diseases, drug treatment, occupation, etc.) or preventive actions, e.g., the diffusion of periconceptional folic acid supplementation at the right timing and dosing.
- Also, considering that the frequency of every single CA is rather low, *data sharing and networking* are very important for the research of any aspect related to CA, but specifically on preventive measures [24].

DISCUSSION

In 2015, countries under the umbrella of United Nations adopted the 2030 Agenda for Sustainable Development and its 17 Sustainable Development Goals [25]. Governments, businesses and civil society together with the United Nations are mobilizing efforts to achieve the Sustainable Development Agenda by 2030. Universal, inclusive and indivisible, the Agenda calls for action by all countries to improve the lives of people everywhere. In particular Goal 3 "Ensure healthy lives and promote well-being for all at all ages" specifically states "Ensuring healthy lives and promoting the well-being for all at all ages is essential to sustainable development. Major progress has been made. However, many more efforts are needed to fully eradicate a wide range of diseases and address many different persistent and emerging health issues."

Primary prevention, therefore, clearly pertains to the domain of *sustainability*. Health system sustainability means that today's efforts to protect and promote health will not reduce resources so to jeopardize the future efforts to provide an equitable and functioning health system to the next generation(s). Hence, owing to primary prevention, the health system will be more sustainable for the society. A science-based primary prevention will reduce both burdens of premature deaths and of chronic disabilities (measureble as DALY) related to CA. This is important also in an ageing society: following the paradygm of "Developmental Origins of Health and Diseases", an effective primary prevention in the early lifestages (starting from intrauterine life, and even preconceptionally) can improve the quality of life of the increasing aged population, and reduce the societal costs for long-term treatment and care of chronic, often invalidating conditions [26].

Data suggest that local and national public health interventions are highly cost-saving. Cuts to public health budgets in high income countries therefore represent a false economy, and are likely to generate billions of euros of additional costs to health services and the wider economy [27].

Sustainable development in the field of health is the goal of meeting the needs of the present without compromising the ability of future generations to cover their own needs. In the fields of food safety and environmental health, for instance, the phasing-out and replacement of hazardous chemicals (such as mutagens, teratogens, endocrine disruptors) are actions that can reduce the burden of disease for generations to come, by enforcing a safer living environment today. Disease prevention must start with improved nutrition and reduced exposure to environmental chemicals during development [26]. Also, sustainable food safety implies the efforts towards the comprehensive knowledge and management of key factors related to to food and diet for protecting and promoting next generation's health; such efforts will contribute to the effectiveness of the overall sustainability policies [28].

Besides sustainability, prevention may also involve the concept of *resilience* at different levels.

Resilience means to adapt the system to changes in order to keep it functioning. The system must be able to adapt itself effectively to changing environments and identify and apply innovative solutions to tackle significant challenges – shortages of expertise/resources in specific areas, unexpected surges in demand with limited resources. In other words, the system needs to build and maintain resilience. Emerging risks, presenting either as new hazards or as new aspects of recognized hazards, call for resilient responses: one example in CA field is the recently recognized teratogen Zika virus [29]. Emerging risks make evident the need for the health system to be able to understand changes and to adapt/modify its responses accordingly. The World Health Organization has considered Zika virus as a case study for emerging risk challenge. European countries can learn from the experience of other regions on how to communicate about Zika and apply these lessons to the European context, as the possible scenarios of Zika outbreaks can show significant differences in terms of size, and composition of the population at risk, cultural and socioeconomic reality and preparedness and response capacity.

To this respect, *health promotion* is important. It is the process of empowering people to increase control over their health and its determinants through health literacy efforts and multi-sectorial action to increase healthy behaviors. This can be addressed to the community-at-large or to populations at increased risk of negative health outcomes. *Disease prevention* and *health promotion* share many goals, and there is considerable overlap between functions. In fact, it is useful to characterize disease prevention services as those primarily concentrated within the health system domain, while health promotion services depend on intersectorial actions and/or are concerned with the social determinants of health.

Primary prevention actions should be targeted based on *scientific evidence*. This statement should not hide

the many uncertainties still existing. A few examples of gaps of knowledge that increase the burden of uncertainties on primary prevention actions regarding CA can be mentioned: in the field of *health interventions*, the benefit-to-risk assessment of flour fortification with folic acid; in the field of *chemical safety,* the possible role of developmental exposures to pollutants in the obesity/diabetes epidemics; in the field of *response to emerging risks*, the role of climate changes on emerging infectious agents (such as Zika virus) and the associated teratogenic risks; in the field of *safe use of medications,* the assessment of possible risks derived from the use of herbal drugs and other widespread "alternative" medicines, in relation to pregnancy; in the field of *safe food,* undertaking actions to identify and characterise emerging risks .

On one hand, the recognized presence of significant gaps of knowledge cannot, by any means, hamper the enforcement of evidence-based actions here and now.

On the other hand, and importantly, prevention needs research and innovation. An uncertainty is a gap of knowledge that can impair the assessment of the benefits introduced by a certain action. Therefore, uncertainties have to be identified and characterized, in order to plan and launch relevant research activities. Recently, it has been stated that for better sustainability and usefulness, it is crucial to refocus and streamline surveillance activities, avoiding a "recreational" data collection, in order to turn the statistically significant results into clinically relevant data. Also, it has been recommended to perform a "triple surveillance" [30]: surveillance of causes, of disease occurrence, and of health outcomes. Such integral surveillance can be a really effective tool for primary prevention of CA.

RECOMMENDATIONS AND CONCLUSIONS

CA, which include an important fraction of rare diseases, are liable to risk reduction by means of science-based primary prevention. In order to achieve an effective primary prevention, the following general recommendations have to be taken into account:

- the professional education and training of all health professionals (not limited to physicians) should provide an adequate room to primary prevention from both the qualitative and quantitative standpoint; this should include epidemiology, social medicine, environmental health, food safety and nutrition, as these themes can be relevant to the work of the majority of health professionals.
- EU Member States should consider the "health-proofing" of all their policies. As pointed out in the above paragraphs, side to the health system, primary prevention involves several other legislative, intervention and scientific domains.
- Health is a fundamental human right; at the same time, it can be considered that the "investment" on primary prevention generates both tangible and intangible benefits. It has been said that "early childhood development is a smart investment" and "the earlier the investment the greater the return" [31]: investing in primary prevention is obviously the earliest possible investment. Nobel Laureate Economist James Heckman's research makes the economic case for early childhood investments starting before birth.

In conclusion, the considerations on CA as an example for primary prevention in the rare diseases field identify the following *highlights:*

1. investing in primary prevention based on scientific evidence is one essential factor supporting sustainability of health systems;
2. primary prevention is a pillar of sustainable development of the society; protection of the early development will enable healthier next generation(s) reaching full adulthood and ageing;
3. in regard of many risk factors (e.g. nutrition, lifestyles, pollution, infections, medications), CA (together with other adverse reproductive outcomes) represent both an important public health issue *per se* as well as an early indicator of public health risks;
4. effective primary prevention requires an integrated "One Health" approach, linking knowledge and action pertaining to human health as well as to physical and social living environments. From the policy standpoint, joint budgeting mechanisms can be envisaged to sustain intersectorial actions, involving the policy domains of health as well as others, e.g., social affairs, education, agriculture, and/or environment;
5. EU Member States (and any country, in fact): should devote resources to strengthen registries, and other tools for systematic data collection and surveillance on CA, so as to better inform national prevention strategies.
6. pillars of primary prevention include science-based risk analysis and surveillance of potential health-damaging factors, citizen's empowerment and education of health professionals;
7. characterization of uncertainties that weaken scientific evidence should target research programmes aimed at supporting the scientific basis of primary prevention;
8. EU Member States should consider the health and equity aspects [32, 33] in all their policies (short, mid and long term). Moreover, The DG SANTE Scientific Committees recommend more dialogue between risk assessors and socio-economists [34].

In summary, primary prevention for CA as well as for other rare diseases, must be considered (better earlier than later) as a pillar of sustainability of health systems and a duty of policy makers with respect to society, which expects that the system provides a better quality of life to all, leaving no one behind.

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